REMARKS

Claims 22-26 and 28-30 are pending and stand rejected by the Examiner. Claims 22-26 and 28-30 have not been amended and are presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the Office Action mailed January 27, 2006. For the reasons set forth below, Applicants respectfully traverse.

Information Disclosure Statement

The Examiner states that the Information Disclosure Statement filed June 20, 2005 including BLAST search results does not provide an alignment or an indication of the percent identity between the claimed sequences and the reference sequences. As such, the Examiner states that the Information Disclosure Statement does not provide sufficient information to determine if the sequences constitute prior art.

Applicants submit herewith a supplemental information disclosure statement listing the PCT patent application publications cited in the BLAST search and enclosing a copy of the European patent application publication and the non-patent literature cited in the BLAST search. Applicants respectfully request that references be considered and entered.

Rejection under 35 U.S.C. § 101 - Utility

The Examiner has maintained the rejection of Claims 22-26 and 28-30 under 35 U.S.C. § 101 as allegedly not being supported by a specific and substantial asserted utility, or a well-established utility. According to the Examiner, there is no asserted utility for antibodies which bind to PRO4380 independent from their use in purifying, detecting, or binding to PRO4380. The Examiner maintains the specification lacks data demonstrating that PRO4380 polypeptides have a substantial utility. In the Office Action, the Examiner acknowledges that the proliferation of kidney mesangial cells is useful. However, the Examiner argues that the asserted utility is not substantial because the threshold used to determine a "positive" in the mesangial cell assay of Example 41 allegedly would not be considered reasonable by one of skill in the art based upon the teachings of the post-filing publication by Rovin et al. According to the Examiner, Rovin teaches that a mesangial cell proliferation assay "has so much variability that even ... a 21% difference is [not significant]." *Office Action* at 6. Therefore, the Examiner argues that "the

specification does not disclose the variability in the sample, so a skilled artisan would not reasonably conclude that PRO4380 induces mesangial cell proliferation." *Office Action* at 6.

Rovin et al. is Irrelevant to the Utility of the Claimed Subject matter

As an initial matter, Applicants note that in the related co-pending U.S. Patent Application No. 10/036,342 which relates to PRO4380 polypeptides and has claims directed to the polypeptides of SEQ ID NO:57, the Examiner has acknowledged that PRO4380 polypeptides have utility based upon the results in Example 41, even in view of Rovin et al. For similar reasons, the claimed antibodies to SEQ ID NO:57 have utility.

In the interest of being fully responsive, Applicants again respectfully submit that "[a]ny reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. 2107.01). An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." Here, there is no reason to doubt or question the utility of PRO4380 polypeptides which tested positive in the mesangial cell proliferation assay.

Example 41 of the specification describes a kidney mesangial cell proliferation assay. PRO4380 tested positive in the assay. Such activity satisfies the utility requirement under § 101. The article by Rovin et al. is irrelevant to the utility of the instant claims. The passage relied upon by the Examiner stated that for the tested compound ciglitazone (at a concentration of 5 μmol/L), the results were not statistically significant. Thus, Rovin et al. merely demonstrates that for the particular tested compound, ciglitazone, it is not possible to tell if the compound caused an outcome that was different from the outcome seen for the control sample. In other words, the particular data point lacked statistical certainty or significance. The statistical significance of the ciglitazone data point in Rovin et al. is completely irrelevant to Applicants assay as described in Example 41, however.

As set forth in Applicants' *Amendment and Response* mailed June 16, 2005, the cited passage from Rovin et al. does not indicate that 21% greater proliferation is not scientifically useful, important, or significant but instead indicates that the individual data point reported

(21%) is statistically unreliable. The lack of significance for the data point concerning ciglitazone in Rovin could be due to several factors, such as experimental error, or the reagents used, compounds tested, etc. -- none of which have anything to do with the reliability of the assay itself. This point is illustrated in the teachings of Rovin et al. that state that ad different compound (troglitazone) showed a "small, but significant increase in proliferation index (18%)." Rovin at p. 1296. Clearly, then, differences in proliferation less than 21% in the assay described in Rovin can be significant. In other words, Rovin has no bearing on the significance of Applicants' data.

Rovin et al. does not contradict the utility of the claimed invention based upon Example 41, nor does Rovin et al. provide reason that would lead one skilled in the art to question the objective truth of Applicants' asserted utilities. As such, the skilled artisan would be convinced, to a reasonable probability, that the asserted utility is true based upon the disclosure of Example 41.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the instant rejection under 35 U.S.C. § 101.

Rejection under 35 U.S.C. § 112, first paragraph - Enablement

The Examiner has maintained the rejection of Claims 22-26 and 28-30 under 35 U.S.C. § 112, first paragraph. According to the Examiner, because the claimed invention is not supported by either a substantial asserted utility, or a well-established utility, one of skill in the art would not known how to use the invention.

Applicants submit that in the discussion of the rejection under 35 U.S.C. § 101, Applicants have established a substantial, specific, and credible utility for the claimed antibodies and the polypeptides to which the antibodies bind. Specifically, the PRO4380 polypeptides, to which the claimed antibodies bind, have utility in inducing mesangial cell proliferation. Therefore, the claimed antibodies have utility.

Rejection under 35 U.S.C. § 102(a)

The Examiner has maintained the rejection of Claims 22-25 as allegedly being anticipated under 35 U.S.C. § 102(a) by WO 99/58660 to Ruben et al. (hereinafter "Ruben"), published

November 18, 1999, as evidenced by Harlow et al. (1988) *Antibodies: A Laboratory Manual.* The Examiner previously asserted that Ruben teaches an amino acid sequence (SEQ ID NO:131) that is 99.6% identical to SEQ ID NO:57 of the instant application, and that Ruben et al. discloses epitopes along the entire length of the protein which can be used for the production of antibodies. Therefore, the Examiner argues that Ruben anticipates the claims. The Examiner argues that the Declaration Under 37 C.F.R. § 1.131 submitted with Applicants' *Amendment and Response* filed June 20, 2005 is insufficient to overcome the Ruben reference. According to the Examiner, the Declaration establishes that Applicants were in possession of the polypeptide of SEQ ID NO:57, but not antibodies to the polypeptide of SEQ ID NO:57 prior to Ruben.

As set forth in M.P.E.P. §715.07(III), there are three ways to show prior invention: (A) actual reduction to practice of the invention prior to the effective date of the reference; or (B) conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent reduction to practice; or (C) conception of the invention prior to the effective date of the reference couple with due diligence from prior to the reference date to the filing date of the application (constructive reduction to practice). Here, the effective filing date of Ruben is November 18, 1999.

As stated in ¶8 of the Declaration Under 37 C.F.R. § 37 C.F.R. § 1.131 previously submitted with Applicants' *Amendment and Response* filed June 20, 2005, Applicants had conceived of SEQ ID NOs:56 and 57 and had established that the polypeptides of SEQ ID NO:57 tested positive in the mesangial cell proliferation assay (Assay 92). Thus, Applicants had actually reduced the polypeptides of SEQ ID NO:57 to practice prior to November 18, 1999 (the publication date of WO 99/58660). Further, ¶10 of the Declaration submitted on June 20, 2005 states that Applicants had "described how to make and use antibodies to the sequences of SEQ ID NO:57" in U.S. Provisional Application No. 60/130,359, filed April 21, 1999. Taken together, the evidence demonstrates that Applicants had constructively reduced the claimed invention to practice (*i.e.,* Applicants had met the requirements to satisfy 35 U.S.C. §112 for the claimed invention) prior to the publication date of WO 99/58660 on November 18, 1999. As such, WO 99/58660 does not describe the invention in a printed publication *before the invention thereof by Applicants*, as required under 35 U.S.C. § 102(a). Thus, Ruben is not prior art under 35 U.S.C. § 102(a).

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejection under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of Claim 22, and has rejected Claims 25, 26, and 30 under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Ruben et al. in view of Holmes et al. (*Current Protocols in Immunology*, pp. 5.35-5.38, 1995). While the Examiner argues that Ruben does not disclose a labeled antibody, he maintains that Holmes teaches conjugation of various labels to antibodies.

As discussed in the section concerning the rejection under 35 U.S.C. § 102(a), Ruben et al. is not available as prior art and does not anticipate under 35 U.S.C. § 102(a), as Applicants had constructively reduced the invention to practice prior to the publication date of Ruben et al. Applicants therefore respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Rejection Under 35 U.S.C. § 102 - Necessitated by Amendment

The Examiner has rejected Claims 25, 28, and 29 under 35 U.S.C. § 102(a) as allegedly being anticipated by WO 99/58660 (Ruben et al.) as evidenced by Harlow et al. ((1998) *Antibodies: A Laboratory Manual*). Claim 25 stands rejected for the reasons set forth in the preceding section regarding rejections maintained under 35 U.S.C. § 102(a). The Examiner argues that new claims 28-29 are rejected because Ruben defines "monoclonal antibody" as including antibody fragments and humanized antibodies, thereby meeting each and every limitation of Claims 28 and 29.

The rejection of Claims 25, 28, and 29 are based on the Examiner's determination that WO 99/58660 is available as prior art under 35 U.S.C. § 102(a). As discussed above, Applicants had reduced the claimed invention to practice prior to the publication date of WO 99/58660, and it is not available as prior art under 35 U.S.C. § 102(a).

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the new rejection of Claims 25, 28 and 29 under 35 U.S.C. § 102(a).

Oath/Declaration

The Examiner states that the oath or declaration is defective, and states that a new oath or declaration in compliance with 37 C.F.R. § 1.67(a). The Examiner argues that the original oath or declaration is defective because of non-initialed and/or non-dated alterations by Zhang and Eaton.

Applicants note that inventors Zhang and Eaton were previously deleted as inventors. Therefore, a new declaration from Zhang and Eaton is not required and the rejection is moot.

Rejection Under 35 U.S.C. § 102(e)

The Examiner has rejected Claims 22-25 and 28-29 as allegedly being anticipated under 35 U.S.C. § 102(e) by U.S. Patent Application Publication 2003/0100051 to Ruben et al., which was published on May 29, 2003, as evidenced by Harlow et al. The Examiner argues that the published application has an effective publication date under § 102(e) of May 12, 1998 or May 18, 1998 based upon 13 provisional applications filed on those dates. The Examiner states that the reference teaches polypeptides that are 97% to the polypeptides of SEQ ID NO:57, as well as monoclonal antibodies to those polypeptides, as well as F(ab') fragments to those polypeptides. According to the Examiner, the teachings of Harlow et al. establish that the antibodies of Ruben would specifically bind to the polypeptides of SEQ ID NO:57, thereby anticipating the claimed subject matter. Applicants respectfully traverse.

As an initial matter, Applicants note that Ruben et al. is a continuation-in-part (CIP) of U.S. Application No. 09/892,877 filed on June 28, 2001, which is a continuation of U.S. Application No. 09/437,658 filed on November 10, 1999, which is a CIP of PCT Application No. PCT/US99/09847 filed on May 6, 1999, which claimed priority to 13 provisional applications filed on May 12, 1998 or May 18, 1998. In view of this, the Examiner argues that the earliest effective publication date under § 102(e) of Ruben et al. is May 12, 1998.

Applicants disagree. Ruben et al. claimed the benefit of an international (PCT) application that was filed before November 29, 2000. Ruben et al. cannot be given the filing date of the PCT application, or the preceding provisional applications, under § 102(e) for prior art purposes. *See* M.P.E.P. § 706.02(f). Therefore, the prior art date of Ruben et al. under § 102(e) is November 10, 1999.

Attached herewith is a Second Declaration of Audrey Goddard, Paul J. Godowski, Austin L. Gurney, James Pan, Colin K. Watanabe and William I. Wood under 37 C.F.R. §1.131 (referred to hereafter as "the Second Declaration of Goddard et al."), which was submitted in related U.S. Patent Application No. 10/036,342. The Second Declaration of Goddard et al. establishes that the presently claimed invention antedates the effective publication date of Ruben et al., November 10, 1999. The Second Declaration is submitted with this response in seven (7) pages with the signature of each inventor on a separate page. Applicants note that inventor Austin Gurney ("Gurney") signed the Second Declaration on the line provided for inventor James Pan ("Pan"). Thus, there are two pages with signatures on the line for James Pan, one signature is by Gurney and the other signature is by Pan.

The Second Declaration of Goddard et al. establishes that the presently claimed subject matter was conceived of and reduced to practice prior to the § 102(e) prior art date of Ruben et al., November 10, 1999. Specifically, the polypeptides of SEQ ID NO:57 had been conceived, and the polypeptides had been shown to induce mesangial cell proliferation prior to November 10, 1999. Further, as indicated in Applicants' provisional patent Application No. 60/130,359, filed April 21, 1999, Applicants had contemplated the claimed antibodies prior to the effective date of Ruben. Taken together, the evidence establishes that Applicants had constructively reduced the claimed invention to practice prior to November 10, 1999. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 U.S.C. § 102(e) be withdrawn.

As set forth in 37 C.F.R. § 1.131, a patent applicant "may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based." *See also*, M.P.E.P. § 715. "The affidavit or declaration must state FACTS and produce such documentary evidence and exhibits in support thereof as are available to show conception and completion of the invention in this country ... at least conception being at a date prior to the effective date of the reference." *See* M.P.E.P. § 715.07 (emphasis in original). The showing of facts must be sufficient to show "conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice." *See id.*

As mentioned above, Ruben et al. has a prior art date under § 102(e) of November 10, 1999. Ruben et al. is cited as a § 102(e) reference because it allegedly discloses an amino acid sequence that is 97% identical to the polypeptides of SEQ ID NO:57, and antibodies that bind thereto. However, as set forth below, Applicants were in possession of SEQ ID NO:57 and the claimed antibodies prior to the § 102(e) date of Ruben et al.

The Declaration and attached Exhibit A demonstrate that polypeptides having the sequence of SEQ ID NO: 57 were conceived by Applicants prior to November 10, 1999. Furthermore, as evidenced by the Declaration and Exhibit B, Applicants reduced the subject matter of the claims to practice prior to the § 102(e) date of Ruben et al., by performing assays to confirm the function of the polypeptide. Finally, as evidenced by Applicants' Provisional Application No. 60/130,359, Applicants had conceived of the claimed antibodies prior to the § 102(e) date of Ruben et al. Therefore, the claimed antibodies were constructively reduced to practice prior to November 10, 1999, the effective date of Ruben et al. In other words, Applicants possessed and reduced the claimed subject matter to practice prior to the publication date of the cited reference.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(e).

Claim Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 22, 25, 26, and 30 as allegedly being unpatentably obvious over U.S. Patent Application Publication No. 2003/0100051 (Ruben et al.) in view of Holmes et al. ((1995) *Current Protocols in Immunology*). As discussed in the above section regarding the rejection under 35 U.S.C. § 102(e), the Examiner maintains that Ruben et al. teaches antibodies and antibody fragments that bind to SEQ ID NO:57. The Examiner further asserts that Holmes et al. teaches conjugation of multiple labels to antibodies for purposes of detection. According the Examiner, it would have been obvious to one skilled in the art to label the antibodies or antibody fragments of Ruben et al. for the purposes of detecting PRO4380.

As discussed above, the Second Declaration of Goddard et al. under 37 C.F.R. § 1.131 and Applicants' U.S. Provisional Application No. 60/130,359 establish that Ruben et al. is not

prior art under 35 U.S.C. § 102, and as such cannot be relied upon to support a rejection under 35 U.S.C. § 103(a). Applicants submit that the rejection under 35 U.S.C. § 103(a) is improper.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

Conclusion

The present application is believed to be in condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/26/05

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